TITLE: CPAP Treatment for Adults with Obstructive Sleep Apnea: Review of the Clinical and Cost-Effectiveness and Guidelines

DATE: 18 November 2013

CONTEXT AND POLICY ISSUES

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent episodes of partial (hypopnea) or complete (apnea) upper airway obstruction during sleep despite ongoing respiratory efforts, resulting in disruption of sleep (arousal).[1] OSA affects 9% of middle-aged men and 3% of women in North America.[2] If left untreated, OSA can lead to fatigue, somnolence, headaches, cardiovascular disease, decreased quality of life, and increased risk of motor vehicle accidents.[2]

The gold standard assessment for OSA is polysomnography, a test that measures neurologic and cardio-respiratory parameters during sleep.[1,2] The frequency of obstructive events measured during polysomnography is reported as the apnea-hypopnea index (AHI).[2] According to the American Academy of Sleep Medicine, the severity of OSA is defined by the following AHI cut-offs: mild, ≥ 5 and < 15 events/hour; moderate, ≥ 15 and < 30 events/hour; severe, ≥ 30 events/hour.[1] OSA is often accompanied by clinical symptoms such as excessive daytime sleepiness, which is most frequently assessed using the Epworth Sleepiness Scale (ESS).[3] The ESS is a questionnaire that has participants rate his or her likelihood of falling asleep in eight different daily situations on a scale of 0 to 24, with higher scores indicating greater sleepiness (ESS ≤ 7, normal sleepiness).[3] The most commonly used objective measures of daytime sleepiness are the Maintenance of Wakefulness Test (MWT), which measures the capacity to stay awake in conditions ideal for falling asleep, and the Multiple Sleep Latency Test (MSLT), which measures the tendency to fall asleep in favourable conditions.[3]

Treatment options for OSA include weight loss, dental devices or oral appliance therapy, surgical procedures, and continuous positive airway pressure (CPAP).[2] CPAP is the mainstay of medical treatment for OSA and involves the use of a pump to deliver air into the nose or mouth via a mask during sleep.[3] Positive pressure is generated by the airflow, which opens up the airway and prevents the soft tissue from collapsing.[3] The effectiveness of CPAP is often limited by poor adherence rates, underscoring the importance of identifying barriers to adherence and developing tailored interventions to improve adherence.[4]

OSA has a substantial economic impact due to an increased risk of cardiovascular disease, decreased quality of life, increased risk of motor vehicle accidents, and loss in occupational productivity.[4] Studies evaluating the effect of CPAP on medical costs are limited and findings are not consistent.[4]

The purpose of this review is to examine the clinical evidence, cost effectiveness and guidelines regarding the use of CPAP treatment for adults with moderate to severe OSA.

RESEARCH QUESTIONS

1. What is the evidence for the clinical effectiveness and safety of CPAP treatment for adults with moderate to severe obstructive sleep apnea?

2. What is the evidence for the cost-effectiveness of CPAP treatment for adults with moderate to severe obstructive sleep apnea?

3. What are the evidence-based guidelines regarding CPAP treatment for adults with moderate to severe obstructive sleep apnea?

KEY FINDINGS

CPAP treatment was found to be effective at improving sleep outcomes in patients with moderate to severe obstructive sleep apnea (OSA), as determined by improvements in Epworth Sleepiness Scale scores. CPAP treatment was found to be more costly than dental devices and lifestyle advice, but lower than commonly accepted cost-effectiveness thresholds. One evidence-based guideline recommends CPAP treatment as initial therapy for patients diagnosed with OSA, with all supporting evidence from trials of patients with moderate to severe OSA.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and October 20, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publication and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with moderate to severe obstructive sleep apnea (diagnosed with AHI criteria)
Intervention	CPAP machine
Comparator	No treatment
Outcomes	Clinical effectiveness (measured by ESS, arousal index, or changes in blood pressure), safety, cost effectiveness, guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic evaluations and evidence-based guidelines.

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or had been included in a selected systematic review, or were published prior to 2009.

Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[5] Non-randomized study quality was evaluated using the Downs and Black instrument.[6] The quality of the included cost-effectiveness studies were assessed using the guidelines for appraisal of economic studies by Drummond et al.[7] Guidelines were assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.[8] A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 757 citations. Upon screening titles and abstracts, 738 citations were excluded and 19 potentially relevant articles were retrieved for full-text review. Three additional reports were retrieved through grey literature searching. Of the 22 potentially relevant reports, 14 did not meet the inclusion criteria. Eight publications were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). One systematic review, four non-randomized studies, two economic evaluations, and one guideline met inclusion criteria.

Summary of Study Characteristics

Details on study characteristics can be found in Appendix 2.

Study design

One systematic review of data from RCTs was included in this review.[3] The systematic review included both parallel and crossover trials, and only the studies using sham-CPAP were double blinded. Of the four non-randomized studies, three were prospective before-and-after studies[9-11]

and one was a retrospective before-and-after study.[12] Two cost-effectiveness analyses[13,14] and one evidence-based guideline[15] were also included in this review.

Country of origin

The systematic review was performed by a group in the UK and included RCTs from multiple countries.[3] Of the non-randomized studies, two were from Australia,[10,11] one was from Canada,[9] and one was from the United States.[12] One economic evaluation each was from the United States[13] and the UK.[14] The guideline was from the United States.[15]

Patient population

The systematic review included 48 RCTs of patients ≥ 16 years of age with OSA measured with a standard severity criterion.[3] Subgroup analyses were conducted according to OSA severity with moderate OSA defined an AHI of 15 to 30 events per hour, and severe OSA was defined as having an AHI of > 30 events per hour.

Among the observational studies, two prospective studies included patients with at least a moderate severity of OSA, as defined by having an AHI of greater than 15 events per hour.[9,11] One prospective study included patients referred to a sleep medicine service with moderate to severe OSA, as defined by having an ESS score of at least 8.[11] The retrospective study included patients with OSA that had an AHI of greater than 5: 31% and 36% of patients had moderate and severe OSA, respectively.[12] One prospective study included patients with type 2 diabetes.[10] In the observational studies, the proportion of male patients ranged from 60% to 86% and the mean age ranged from 41 to 66 years.[9-12] The average BMI in the studies ranged from 28.7 to 34.7 kg/m^2.[9-12]

Both economic evaluations used a base case population of males aged 50 years.[13,14] One economic evaluation considered the population that had a 50% pretest probability of having moderate to severe OSA, defined as an AHI of greater or equal to 15 events per hour.[13] The other economic evaluation did not specify the severity of OSA, but analyzed the cost data according to disease severity.[14]

The evidence-based guideline focused on adults with OSA.[15]

Interventions and comparators

The systematic review, non-randomized studies and economic evaluations focused on CPAP treatment as the main intervention. The systematic review looked at best supportive care, sham CPAP and dental devices as comparators.[3] There were no comparators used in the prospective observational studies.[9-11] The retrospective observational study used oral appliance as a comparator.[12] The economic evaluations compared CPAP with either no treatment[13] or dental devices and lifestyle advice.[14]

Outcomes measured

The systematic review[3] and prospective observational studies[9-11] used ESS as a clinical endpoint, comparing scores before and after CPAP treatment. Other outcomes assessed in the observational studies included the respiratory disturbance index (RDI),[9] and oxygen saturation

(SpO_2),[9] the Maintenance of Wakefulness Test (MWT),[11] and the reduction in AHI before and after CPAP treatment.[12]

The economic evaluations estimated the cost-effectiveness of CPAP when compared to no treatment[13] or dental devices and lifestyle advice.[14] One economic evaluation was from the US third party payer perspective[13] and one economic evaluation was from the UK health care payer perspective.[14] Data on the effect of untreated OSA on the incidence of motor vehicle collisions and cardiovascular events were estimated from the literature.[13,14] One economic evaluation reported costs in USD using prices from 2008.[13] The other economic evaluation reported prices in UK pounds using prices from 2005 to 2006.[14]

The guideline provided recommendations for the treatment of OSA in adults based on an Agency for Healthcare Research and Quality (AHRQ) systematic review of the literature on the effect of OSA treatment on sleep study measures, measures of cardiovascular and diabetes status, and quality of life.[15] The AHRQ review included prospective comparative studies and RCTs. The guidelines supplemented the AHRQ review with observational studies in humans reporting death or cardiovascular illness associated with OSA treatment strategies and more recent RCTs.[15]

Summary of Critical Appraisal

Details on critical appraisal can be found in Appendix 3.

The systematic review employed a comprehensive literature search, screened in duplicate, and assessed the scientific quality of included studies. A summary of the characteristics of the included studies was provided.[3] The risk of publication bias was not formally assessed and it was unclear whether grey literature was included in the search strategy. The included RCTs were assessed for whether they had an adequate method of allocation concealment and whether there was blinding of participants. Only in the studies comparing CPAP to sham-CPAP could participants be blinded. It was not possible to have appropriate blinding for studies using dental devices as comparators, and this may bias the outcomes due to the subjective nature of the ESS. The data from the RCTs were pooled using a random effects meta-analysis which was considered appropriate. The sample sizes of the included RCTs were generally small (maximum N = 118).

In the prospective observational studies, the intervention was clearly described.[9-11] One study employed a control group of healthy subjects, but this was so that they can compare neuropsychological outcomes of OSA patients to a healthy cohort.[9] No observational studies used a control group that received sham-CPAP, so it was unclear whether OSA patients would improve due to a placebo effect over time.[9-12] The lack of blinding in all of the studies may be problematic, as the ESS is a subjective assessment of sleepiness. However, sham-CPAP was not always possible due to ethical considerations. CPAP compliance was assessed in all of the prospective observational studies. In the retrospective observational study, the length of CPAP treatment was not specified. Patients who received oral appliance therapy did so after CPAP therapy, so the results may not be generalizable to patients who had not received CPAP therapy in the past.[12] There was also no reporting of CPAP compliance and the study was conducted using data from a single clinic, which may limit generalizability of the results.[12]

Both economic evaluations were conducted in a similar manner in that a literature review of the impact of OSA on sleep outcomes, motor vehicle collisions and cardiovascular events was

performed.[13,14] The main limitation of the economic evaluations was the availability of data used to generate the model. The majority of patients in the studies were middle-aged men, which may limit generalizability to other patient populations. All of the economic evaluations were conducted in countries outside of Canada and use prices from 2005 to 2008 that may be outdated.

The guideline had was based on a systematic review that had clearly defined selection criteria, methodologies, and a grading system for recommendations.[15] Most of the literature identified was of moderate-quality as determined by the study design, risk of bias, and appropriate outcome measures and reporting. Patient preference and views were not taken into consideration and the costs and barriers to guideline implementation were not evaluated or reported. It was unclear whether the guidelines were peer reviewed.

Summary of Findings

Details on study findings can be found in Appendix 4.

<u>What is the evidence for the clinical effectiveness and safety of CPAP treatment for adults with moderate to severe obstructive sleep apnea?</u>

One systematic review performed subgroup analyses according to OSA severity to determine the effectiveness of CPAP versus placebo or usual care on daytime sleepiness according to improvements in ESS scores.[3] For patients with moderate OSA, pooled results from seven trials found that there was a statistically significant improvement in ESS score in favour of CPAP (mean difference -2.04, 95% confidence interval [CI] -2.99 to -1.09). For patients with severe OSA, pooled results from fourteen trials found that there was a statistically significant improvement in ESS score in favour of CPAP (mean difference -3.41, 95% CI -4.56 to -2.26). The benefit of CPAP compared to placebo or usual care was larger in the trials that included patients with severe OSA. There was a high degree of statistical heterogeneity among the pooled trials (I^2 65% to 71%) and five potential sources of this between study variability were baseline disease severity, baseline daytime sleepiness, study design, type of placebo, and study quality. The systematic review also compared CPAP and dental devices and found that for patients with moderate OSA, pooled results from six trials found no statistically significant difference in the impact on ESS scores (mean difference -0.85, 95% CI -2.11 to 0.41).

The three prospective observational studies evaluated the effectiveness of CPAP in patients with moderate to severe OSA using a before-and-after design.[9-11] One study found that the mean ESS score after three months of CPAP treatment was statistically significantly better than before treatment (mean difference -6.1, P < 0.001).[9] The proportion of patients with an ESS score of greater than 10, which was considered to be clinically significant, dropped from 76% to 30% after CPAP treatment.[9] The same study found that there was a statistically significant improvement in mean respiratory disturbance index (P < 0.001) and mean oxygen saturation (P < 0.01) after CPAP treatment compared to before treatment.[9] Another prospective observational study found that there was a statistically significant improvement in the median ESS score after one and three months of CPAP treatment compared to before treatment (P < 0.001).[10] This study also found an improvement in systolic and diastolic blood pressure after CPAP treatment.[10] The third observational study found high variability in patient compliance with CPAP treatment, and analyzed sleep outcomes according to CPAP adherence.[11] The proportion of patients that achieved a normal ESS score, defined as a score of less than 10, increased after

three months of CPAP treatment.[11] There was a clear dose-response relationship for CPAP therapy in that a greater proportion of patients achieved a normal ESS score if they had an average of at least 7 hours of CPAP treatment per night compared to if they had on average less than or equal to 2 hours of treatment per night (80.6% versus 35.9%, respectively).[11] Unlike for ESS scores, there was no association between CPAP adherence and MWT scores.[11] All three prospective observational studies assessed CPAP compliance using a built-in smart card,[9] or a built in device counter.[10,11]

The retrospective observational study found that CPAP treatment improved the AHI significantly when compared to oral appliance in patients with severe OSA (mean difference -5.88, 95% CI -8.95 to -2.82, P < 0.001), but not in patients with moderate OSA.[12] Compliance to CPAP therapy was not measured or reported.

<u>What is the evidence for the cost-effectiveness of CPAP treatment for adults with moderate to severe obstructive sleep apnea?</u>

One economic evaluation estimated the cost-effectiveness of CPAP treatment compared to no treatment.[13] A Markov model was created to compare costs and effectiveness over a 10-year interval and the expected lifetime of the patient, assuming that OSA treatment would reduce motor vehicle collisions and cardiovascular events. The base case population was a hypothetical cohort of 50 year old males with a 50% pretest probability of having moderate to severe OSA. Costs were presented in 2008 prices in USD. Using the base case scenario, the incremental cost-effectiveness ratio (ICER) for CPAP treatment was $15,915 per quality-adjusted life year (QALY) gained for the lifetime horizon. Sensitivity analyses found that these results were not sensitive to gender, age or CPAP adherence. The results were most sensitive to the cost of CPAP therapy.

Another economic evaluation estimated the cost-effectiveness of CPAP compared to dental devices or lifestyle advice.[14] A Markov model was created to compare these interventions over the expected lifetime of the patient, incorporating the impact of treatments on daytime sleepiness, blood pressure, and health-related quality of life. Daytime sleepiness can increase the risk of road traffic accidents, and blood pressure may affect the incidence of cardiovascular events, and so these events were also included in the model. Costs were presented in 2005 to 2006 prices in UK pounds. The ICER for CPAP treatment compared to dental devices and lifestyle advice was £20,585 per QALY for patients with mild OSA, £9,391 per QALY for patients with moderate OSA, and £4,413 per QALY for patients with severe OSA. The study concluded that CPAP therapy was cost-effective compared to dental devices or lifestyle advice for patients with moderate to severe OSA, but not patients with mild OSA. The results were most sensitive to the cost of CPAP therapy.

<u>What are the evidence-based guidelines regarding CPAP treatment for adults with moderate to severe obstructive sleep apnea?</u>

One evidence-based guideline was identified from the American College of Physicians.[15] The American College of Physicians recommends "continuous positive airway pressure as initial therapy for patients diagnosed with obstructive sleep apnea." [Strong recommendation, moderate-quality evidence]. This guidance was developed from a systematic review of the literature. CPAP was found to be the most extensively studied therapy and improved ESS scores, reduced AHI and arousal index scores, and increased oxygen saturation in patients with

at least moderate OSA. However, the literature did not show that CPAP increased quality of life, and evidence on the effect of CPAP on cardiovascular disease, hypertension, and type 2 diabetes was insufficient.[15]

Limitations

In the systematic review, there was moderate to high heterogeneity among trials in the pooled analyses which limits the confidence in the pooled estimates. However, sensitivity analyses suggested that the benefit of CPAP on daytime sleepiness was robust. In addition, the included studies in the systematic review were not all blinded, particularly in studies that did not use sham-CPAP as a comparator. In the non-randomized studies, a before-and-after design was used with no sham-CPAP control group or blinding and may overestimate the benefit of CPAP treatment on daytime sleepiness symptoms. Although CPAP treatment was associated with statistically significant improvement in ESS scores, the minimal clinically important difference (MCID) for ESS is not known, thus the clinical importance of the differences reported are unclear.

The duration of CPAP treatment in the observational studies was three months, therefore longer-term effectiveness of CPAP treatment in patients with moderate to severe OSA is lacking. The definition of moderate to severe OSA was generally consistent among the included studies (AHI ≥ 15), however in one observational study, the AHI range was not defined in the patients and so it was unclear whether enrolled patients met this criterion.

The majority of patients enrolled in the included studies were male, and this is also reflected in the economic evaluations where the base case scenarios were 50 year old males. This may limit the generalizability of the results to a broader population. There were no economic evaluations identified that were conducted in the context of the Canadian healthcare system, and the included studies used prices from 2005 to 2008 that may be outdated. It may be difficult to generalize results from other countries to the Canadian context.

There was only one American evidence-based guideline that was identified, and the recommendations were not specific to patients with moderate to severe OSA. However, the evidence supporting the recommendation was relevant to patients with at least moderate OSA, and therefore the guideline was included in this review.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

According to one systematic review of RCTs and four non-randomized studies, CPAP treatment appears to be effective at improving sleep outcomes in patients with moderate to severe OSA, as determined by improvements in ESS scores, however the clinical importance of the differences found was unclear.

Results from US and UK economic evaluations found CPAP treatment to be more costly than dental devices and lifestyle advice, but lower than commonly accepted cost-effectiveness thresholds. However, the generalizability of these findings to the Canadian healthcare system may be limited.

The American College of Physicians guideline recommended CPAP treatment as initial therapy for patients diagnosed with OSA.

The included clinical studies were generally of moderate quality. The lack of control groups and blinding were major limitations of the observational studies, as the main sleep outcome was subjective and reported by the patient. There were no economic evaluations or guidelines identified in the Canadian context.

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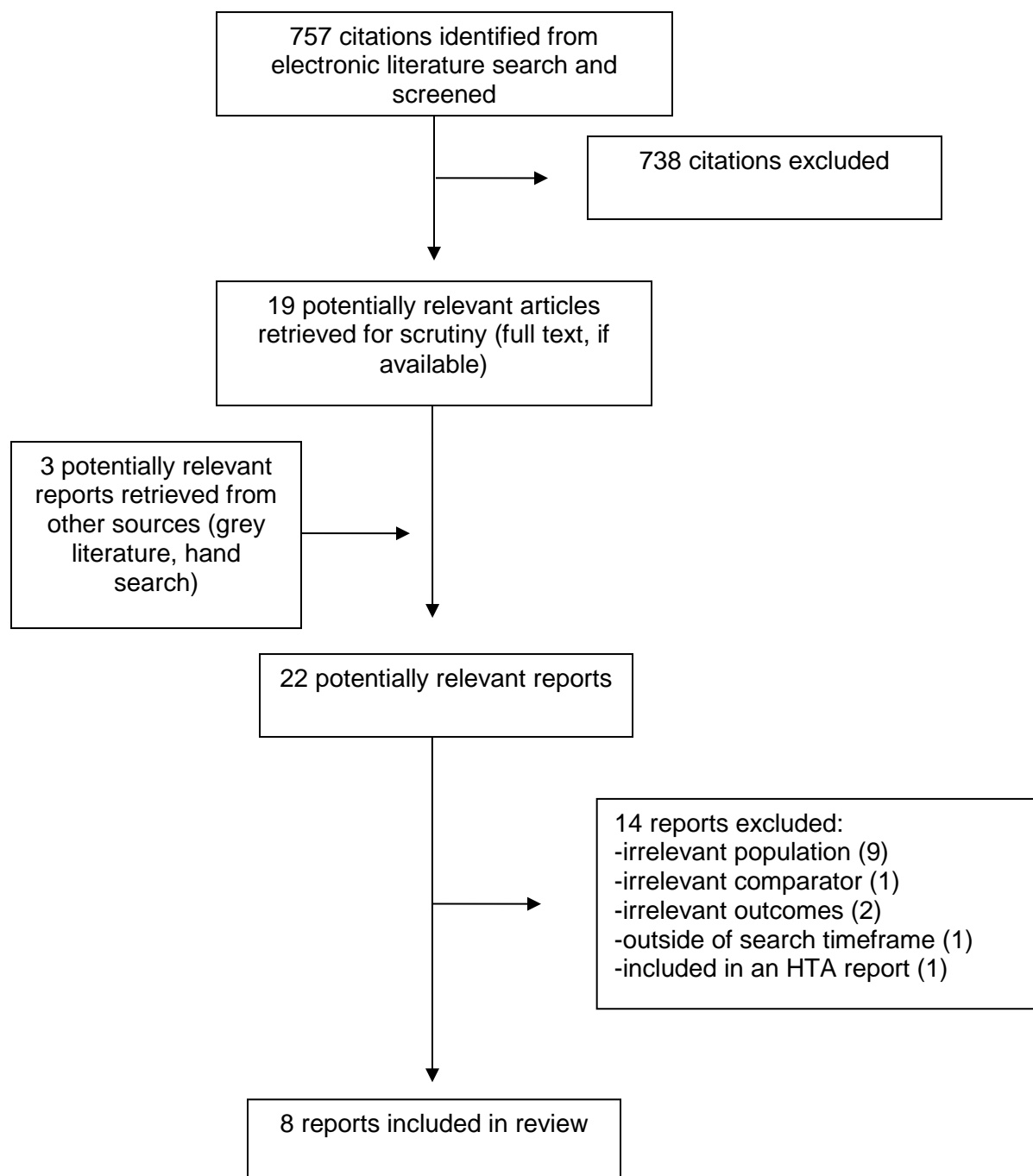Canadian Agency for Drugs and Technologies in Health
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APPENDIX 1: Selection of Included Studies

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│ 757 citations identified from   │
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APPENDIX 2: Summary of Study Characteristics

Characteristics of included systematic reviews and nonrandomized studies

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator(s)	Clinical Outcomes Measured
McDaid[3] 2009 UK	Systematic review (as part of an HTA)	48 RCTs including adults (16 years and older) with a diagnosis of OSA measured with a standard severity criterion -population subgroup: baseline disease severity as classified using the AHI (mild, 5-14/hour; moderate, 15-30/h; severe, > 30/h)	CPAP (fixed or autotitrating) treatment for at least one week duration	Best supportive/ usual care Placebo (placebo pill, sham CPAP) Dental devices	Subjective sleepiness as assessed by the ESS
Lau[9] 2013 Canada	Prospective, observational study (before-and-after design)	37 patients with a previous diagnosis of moderate to severe OSA (AHI>15/h) who were on treatment with CPAP for at least 3 months with a compliance of at least 4 h/night for 80% of the week (self-report verified by built-in smart card for 73% of patients): mean age 57.9 ± 9.5 years; 59.5% male; mean BMI 33.5 ± 7.4 kg/m^2; mean time since OSA diagnosis 25.6 ± 21.1 months; mean duration of CPAP treatment 17.8 ± 11.4 months 27 healthy control participants: mean age 56.7 ± 10.5 years; 29.6% male; mean BMI 15.7 ± 3.2 kg/m^2	CPAP treatment for at least 3 months – compliance verified by built-in smart card	None	ESS, RDI, SpO_2, psychosocial functioning
Myhill[10] 2012 Australia	Prospective, observational study (before-and-after design)	59 participants of the Fremantle Diabetes Phase II Study (with Type 2 Diabetes) who were diagnosed with	CPAP treatment for 3 months - compliance assessed from the device	None	ESS, blood pressure

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator(s)	Clinical Outcomes Measured
		OSA of at least a moderate severity by polysomnography (AHI > 15/h) – 44 participants completed the study: mean age 66.1 ± 8.8 years; 61.4% male; mean BMI 33.6 ± 5.5 kg/m^2; median AHI 38 (IQR 27 to 58); median ESS 9 (IQR 6 to 13)	counter at 1 and 3 months after initiation		
Antic[11] 2011 Australia	Prospective, multicenter, observational study (before and after design) - original study was an RCT comparing nurse-led and specialist-led care of pts with OSA, results of both groups were analyzed together in this study	174 patients referred to a sleep medicine service with moderate to severe OSA, defined as an ESS score of at least 8: mean age 50.1 ± 12.0 years; 74.9% men; mean BMI 34.7 ± 6.8 kg/m^2; mean ESS score 13.4 ± 4.0; mean SF-36 total score 99.0 ± 8.6	CPAP treatment (S6 Elite lightweight, ResMed) for 3 months – compliance measured by a built-in CPAP meter	None	ESS, MWT
Holley[12] 2011 USA	Retrospective study in a single clinic (before and after design)	497 patients who were given an oral appliance and had an AHI>5 as determined by overnight polysomnography (378 patients had both CPAP and oral appliance titrations available for comparison): mean age 41.3 ± 9.0 years; 86.4% men; mean BMI 28.7 ± 4.4 kg/m^2; mean ESS score 12.9 ± 5.1; mean AHI 30.0 ± 24.8 (OSA severity: 33.4% mild; 30.8% moderate; 35.8% severe)	CPAP	Oral appliance – Thorton Adjustable Positioner (Airway Management, Inc)	AHI reduction

AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; IQR = interquartile range; MWT = Maintenance of Wakefulness Test; OSA = obstructive sleep apnea; RCT = randomized controlled trial; RDI = respiratory disturbance index; SF-36 = short form 36; SpO$_2$ = oxygen saturation

Characteristics of included economic evaluations

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient Population	Intervention and Comparator	Comments
Pietzsch[13] 2010 USA	Cost-effectiveness analysis US third party payer perspective (presented in 2008 USD)	Base case population: a hypothetical average cohort of 50 year old males with a 50% pretest probability of having moderate to severe OSA (AHI≥15 events/h) – considered women and alternative ages in sensitivity analyses	CPAP versus no treatment	Markov model Age- and gender-specific all-cause mortality was estimated using the 2004 US life tables The magnitude of effects of untreated moderate to severe OSA on the incident rates of motor vehicle collisions, myocardial infarction, stroke and hypertension were estimated from the literature Timeframe: 10 years and patient lifetime All costs were reported for the price year 2008 (USD) Main outcome: QALYs Probabilistic sensitivity analyses were performed
Weatherly[14] 2009 UK	Cost-effectiveness analysis Part of a full HTA[3] National Health Service and Personal Social Services perspective (health care payer perspective).	Base case population: a male cohort aged 50 years old with OSA	CPAP versus dental devices or lifestyle advice	Markov model The evidence used to estimate the parameters of the model was obtained from a systematic review.[3] Individual patient data was obtained from other literature. Timeline: patient lifetime All costs were reported using 2005-2006 prices. Main outcome: QALYs Probabilistic sensitivity analyses were performed.

Characteristics of included evidence-based guidelines

First Author, Publication Year, Country	Objective	Intervention	Outcome
American College of Physicians[15] 2013 USA	To present the evidence and provide clinical recommendations on the management of obstructive sleep apnea in adults.	Positive airway pressure machines	Cardiovascular disease, sleep study measures, measures of cardiovascular status, measures of diabetes status, quality of life

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Systematic reviews		
McDaid[3,16] 2009	• Comprehensive literature search based on pre-defined criteria • Duplicate study selection and data extraction employed • Summary of study characteristics provided • Scientific quality and risk of bias of included studies assessed and documented • List of excluded studies provided	• Risk of publication bias not formally assessed • Unclear whether grey literature was included in the search strategy
Non-randomized studies		
Lau[9] 2013 Prospective study	• A control group of health subjects was used • Inclusion criteria was clearly described • CPAP compliance was measured	• Patients received different lengths of CPAP treatment (range 3 to 47 months) • No randomization or blinding
Myhill[10] 2012 Prospective study	• Intervention was clearly described • Prospective study • CPAP compliance was measured	• No control group (due to ethical considerations) • No randomization or blinding • There was an insufficient number of patients enrolled based on the power calculation (N=59 instead of 100) • Patient population was specific to those with Type 2 Diabetes, limiting generalizability to other patients with OSA
Antic[11] 2011 Prospective study	• Intervention and outcome measures were clearly described • Prospective study • CPAP compliance was measured	• No control group • No randomization or blinding • AHI was not reported as an enrollment criteria or outcome measure
Holley[12] 2011 Retrospective study	• Large sample size • Intervention and outcomes measures were clearly described	• No randomization or blinding • No control group • Retrospective study • Study was taken from a single clinic, may not be generalizable to a wider range of practices • CPAP compliance not measured • Length of CPAP treatment not reported
Economic evaluations		
Pietzsch[13] 2010	• The research question was clearly stated • The source of effectiveness data was reported • The study used a decision tree and Markov model	• The analysis used cost data from 2008 specifically in the USA, which limits generalizability to other countries and may not representative of more current costs • The study population was limited to patients with OSA of average cardiovascular risk
Weatherly[14] 2009	• The research question was clearly stated • The source of effectiveness data was reported • The study used a decision tree and Markov model	• The analysis used cost data from 2005-2006 in the UK, which limits generalizability to other countries • The assumption was made that ESS impacts HRQoL, but other measures may

First Author, Publication Year	Strengths	Limitations
		also impact HRQoL independent of ESS • The majority of the study population in the trials were middle-aged men, therefore it is unclear whether therapeutic benefits are similar in other groups
Guideline		
American College of Physicians[15] 2013	• Objectives and patient population clearly described • Selection criteria and methodologies and evaluation criteria clearly described • Included studies were appraised for quality • Recommendations were graded according to a defined grading system	• Patient preference and views not taken into consideration • Costs and barriers of guideline implementation not evaluated • It was unclear whether the guidelines were peer reviewed
AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea		

APPENDIX 4: Summary of Findings

Summary of systematic reviews, non-randomized studies and economic evaluations

First Author, Publication Year	Main Study Findings	Author's Conclusions
Systematic reviews		
McDaid[3] 2009	Studies were grouped by disease severity (AHI) at baseline for subgroup analyses. CPAP versus placebo or usual care For patients with moderate OSA (AHI 15-30 events/hour), the estimate of treatment effect was based on results from 7 trials. There was a statistically significant improvement in ESS score in favour of CPAP (mean difference = -2.04 (95% CI -2.99 to -1.09). Heterogeneity was moderate (I^2 = 65.4%) For patients with severe OSA (AHI > 30 events/hour), the estimate of treatment effect was based on results from 14 trials. There was a statistically significant improvement in ESS score in favour of CPAP (mean difference = -3.41 (95% CI -4.56 to -2.26). Heterogeneity was high (I^2 = 71.0%). The benefit of CPAP was largest in the trials with patients with severe OSA. There was a high degree of statistical heterogeneity. CPAP versus dental devices For patients with moderate OSA, the estimate of treatment effect was based on results from 6 trials. There was no statistically significant difference in the impact on ESS scores between CPAP and dental devices (mean difference = -0.85, 95% CI -2.11 to 0.41)	"Overall, CPAP reduced daytime sleepiness by a small amount compared with control; the effect probably varies among different groups of people…When studies were subgrouped by disease severity at baseline, as measured by the AHI, there was a broadly similar trend." (p. 24-25)
Non-randomized studies		
Lau[9] 2013	Mean CPAP compliance The percentage of days with CPAP usage >4 hours in the last 3 months was 96.4±5.6 among OSA patients. Mean ESS (SD) OSA patients Before CPAP treatment: 14.4 (5.2) After CPAP treatment: 8.3 (4.5) Healthy Controls: 6.6 (4.7) Before versus After: p<0.001 Proportion of patients with ESS>10 (clinically significant range), %	"The percentage of individuals in the OSA group with self-reports of pathological sleepiness dropped from 76% to 30% after treatment, with a significant mean change of 6.1. It could be concluded that sleepiness was significantly reduced in the OSA group after CPAP treatment, although one-third of individuals continued to show excessive sleepiness during the day (compared to 15% of controls). Given that sleepiness was found to consistently predict psychosocial outcomes in this study, the question of what predicts residual sleepiness in treated individuals with OSA is relevant." (p. 5)

First Author, Publication Year	Main Study Findings	Author's Conclusions
	OSA patients Before CPAP treatment: 75.7 After CPAP treatment: 29.7 Healthy Controls: 14.8 Mean Pittsburg Sleep Quality Index global score, PSQI (SD) OSA patients Before CPAP treatment: 8.5 (3.3) After CPAP treatment: 4.4 (2.4) Healthy Controls: 4.6 (2.8) Before versus After: $p<0.001$ Mean respiratory disturbance index, RDI (SD) OSA patients Before CPAP treatment: 42.2 (24.9) After CPAP treatment:1.7 (1.5) Healthy Controls: 4.0 (3.4) Before versus After: $p<0.001$ Mean oxygen saturation, SpO_2 (SD) OSA patients Before CPAP treatment: 93.7 (3.5) After CPAP treatment: 95.7 (1.6) Healthy Controls: 95.7 (0.9) Before versus After: $p<0.01$	
Myhill[10] 2012	CPAP compliance Compliance data was available for 42 of the 44 participants who completed the study and was found to be 5.4 ± 1.6 h/night. Median ESS (IQR) Baseline: 9 (6, 13) After one month of CPAP: 4 (3, 6); mean difference = -4.7, 95% CI -6.4 to -3.1, $p<0.001$ After 3 months of CPAP: 4 (2, 7); $p<0.001$ Mean systolic blood pressure ± SD Baseline: 149 ± 23 mm Hg After 3 months of CPAP: 140 ± 18 mm Hg, $p=0.005$ Mean diastolic blood pressure ± SD Baseline: 80 ± 12 mm Hg After 3 months of CPAP: 73 ± 13 mm Hg, $p=0.007$	"The present data show that a 3-month course of CPAP improves blood pressure and lowers pulse rate significantly in type 2 diabetic patients with at least moderate OSA…Our subjects were able to achieve and maintain and average of more than 5 h CPAP use nightly during the 3 months of the study, and this was reflected in a significant improvement in ESS." (p. 4216)
Antic[11] 2011	CPAP compliance CPAP compliance was highly variable, with a coefficient of variation exceeding 50%. Proportion of patients that achieved a normal ESS score (≤10), n/N (%)	"There were markedly different results for tests of subjective and objective sleepiness/vigilance. A clear dose-response relationship for CPAP therapy was evidence in the posttreatment ESS results, whereas no dose-response relationship was evidence for

First Author, Publication Year	Main Study Findings	Author's Conclusions
	Before treatment: 44/168 (26.2) Total: 100/168 (59.5) Mean ≥7 CPAP hours/night: 25/31 (80.6) Mean ≤2 CPAP hours/night: 14/39 (35.9) The ESS showed significant dose-dependent improvement following CPAP treatment (p<0.001) with significantly greater improvement in more-adherent patients (compliance and treatment by compliance effects p=0.018 and p=0.004, respectively). Proportion of patients that achieved a normal MWT score (>26.1 min), n/N (%) Total: 84/123 (68.3) Mean ≥7 CPAP hours/night: 17/25 (68.0) Mean ≤2 CPAP hours/night: 14/23 (60.9) This study measured neurobehavioral outcomes including FOSQ scores, SF-36 scores, executive function and reaction times. As these were not specifically sleep outcomes, they are not reported in detail here.	posttreatment MWT sleep latencies. By study design, a high proportion of patients were in the abnormal ESS range at baseline (74%), and this proportion decreased significantly, to 42% after treatment" (p. 116)

Holley[12] 2011	Baseline characteristics
	Mean AHI: 30.0 ± 24.8
	Mean SpO_2 nadir: 83.8 ± 7.5
	
	Oral appliance (mean ± SD)
	Duration of treatment: 221.4 ± 124.1 days
	Final AHI: 8.3 ± 11.4
	Final SpO_2 nadir: 85.1 ± 7.3
	% patients with AHI<5: 53.8
	    Mild OSA (n=186): 69.9
	    Moderate OSA (n=144): 47.9
	    Severe OSA (n=167): 41.9
	% patients with AHI<10: 73.9
	    Mild OSA: 86.0
	    Moderate OSA: 75.0
	    Severe OSA: 60.5
	
	CPAP (mean ± SD)
	Duration of treatment: not reported
	Final AHI: 5.6 ± 10.9
	% patients with AHI<5: 69.1
	    Mild OSA (n=113): 76.2
	    Moderate OSA (n=114): 70.7
	    Severe OSA (n=151): 62.9
	% patients with AHI<10: 84.3
	    Mild OSA: 85.7
	    Moderate OSA: 87.7
	    Severe OSA: 80.1
		"We found that the majority of patients using an adjusted oral appliance (aOA) achieved an AHI <5 on the PSG titration, and the ESS decreased significantly after an aOA was prescribed. In multivariate analysis, only AHI remained a significant predictor of aOA success. Although CPAP was superior for patients with severe OSA, the difference in AHI reduction between the aOA and CPAP was not significant for patients with mild and moderate disease…Base on our results, an aOA would be a reasonable, first-line alternative to CPAP for patients with mild disease. For patients with moderate to severe disease, our higher success rates call into question the recommendation that a CPAP failure is required prior to using an adjustable OA. Future studies should focus on measuring aOA adherence and side effects along with patient treatment preferences so that a comprehensive comparison with CPAP can be conducted." (p. 1514)

First Author, Publication Year	Main Study Findings	Author's Conclusions
	<u>CPAP versus Oral Appliance</u> CPAP improved the AHI by -3.43 (95% CI -1.88 to -4.99, p<0.001) when compared to oral appliance. Differences were calculated based on severity of the disease. Mild OSA: -1.9 (95% CI -3.8 to 0.02, p=0.053) Moderate OSA: -1.7 (95% CI -4.0 to 0.7, p=0.17) Severe OSA: -5.88 (95% CI -8.95 to -2.82, p<0.001) <u>CPAP versus Oral Appliance for proportion of patients achieving AHI<5</u> Overall: 70.1% vs. 51.6% (p<0.001) Mild OSA: 76.2% vs. 62.3% (p=0.15) Moderate OSA: 71.0% vs. 50.8% (p<0.001) Severe OSA: 63.4% vs. 39.9% (p<0.001)	
Economic evaluations		
Pietzsch[13] 2010	CPAP therapy reduces the average number of motor vehicle collisions and lifetime risk of cardiovascular events. These parameters were used to calculate the QALYs. <u>CPAP treatment vs no treatment</u> Base Case: $15,915/QALY Perfect compliance: $15,769/QALY Low compliance (double patients who never try therapy and double quit rate): $16,112/QALY <u>Sensitivity analyses</u> The results were not sensitive to gender or cohort age or compliance. The results were most sensitive when the cost of CPAP treatment was varied, when only benefits associated with reduced daytime sleepiness were included (no motor vehicle collision or cardiovascular benefit), and when the utility gains from reduced daytime sleepiness were excluded. The results were generally stable within a range of sensitivity analyses.	"Using a mathematical model of OSA, we found that CPAP therapy increases life expectancy and quality-adjusted life expectancy, and reduces the rate of fatal and non-fatal motor vehicle collision, myocardial infarction, and stroke. We also found that CPAP therapy is cost-effective for men and women at all ages considered (30-70 years) who have already been diagnosed with moderate-to-severe OSA with ICERs between $15,478 and $22,348 per QALY gained, which are lower than the ratios for treatments and technologies thought to be of good value and below the commonly used thresholds for determining cost effectiveness in the US." (p. 706)
Weatherly[14] 2009	CPAP reduces the number of road traffic accidents and cardiovascular events, and improves health related quality of life. These parameters were used to calculate the QALYs. CPAP machine was estimated to have a device life of 7 years, and dental devices were estimated to last for 2 years. CPAP was associated with higher costs and	"The analysis presents reasonably strong evidence to suggest that, at a cost-effectiveness threshold of £20,000 per QALY, CPAP is cost-effective compared with dental devices or lifestyle advice with one exception: the mild baseline severity subgroup. The results were not sensitive to leaving CVE [cardiovascular events] and RTA [road traffic accidents] events from the model, thus the ESS is driving the cost-effectiveness." (p. 32)

First Author, Publication Year	Main Study Findings	Author's Conclusions
	higher QALYs compared with treatment with dental devices or lifestyle advice. CPAP versus dental devices Base Case: £3,899/QALY CPAP versus dental devices and lifestyle advice Mild OSA: £20,585 Moderate OSA: £9,391 Severe OSA: £4,413 Sensitivity analyses The largest effect on the CPAP ICER came from applying the higher acquisition cost for the treatment.	
ESS = Epworth Sleepiness Scale; ICER = incremental cost-effectiveness ratio; IQR = interquartile range; OSA = obstructive sleep apnea; QALY = quality-adjusted life year; SD = standard deviation		

Summary of guidelines

Guideline Society, Country, Author, Year, Indication	Recommendations
American College of Physicians[15] 2013 USA Adults with obstructive sleep apnea	"ACP recommends continuous positive airway pressure treatment as initial therapy for patients diagnosed with OSA." [Strong recommendation, moderate-quality evidence] "In patients with excessive daytime sleepiness who have been diagnosed with OSA, CPAP is the most extensively studied therapy. This treatment has been shown to improve ESS scores, reduce AHI and arousal index scores, and increase oxygen saturation. However, CPAP has not been shown to increased quality of life. Evidence on the effect of CPAP on cardiovascular disease, hypertension, and type 2 diabetes was insufficient. Studies have evaluated various alternative CPAP modifications. Fixed and auto-CPAP, as well as C-Flex, have similar adherence and efficacy. Data were insufficient to determine the comparative efficacy of other CPAP modifications. Greater AHI and ESS scores were generally associated with better adherence to CPAP."